Remarks

Claims 56-114 are pending in the subject application. By this Amendment, Applicants have canceled claims 81-84. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 56-80 and 85-114 are currently before the Examiner with claims 59, 60, 86-110, 112 and 114 standing withdrawn from consideration. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objection to the drawings and claim and the rejections under 35 U.S.C. §§ 112, first and second paragraphs, 102(b) and 103(a).

Claims 68-85 and 113 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action argues that the as-filed specification fails to enable the administration of the claimed compositions to any patient, including any elderly patient nor for prophylactic treatment. Applicants respectfully assert that the claims as filed are enabled and that the Office Action improperly focuses on aspects of the claims that pertain to the intended use of the compositions (*e.g.*, for administration to a human patient for prophylactic or therapeutic stimulation of B or T lymphocyte development and proliferation, for enhancement of global or specific immuno-reconstitution, for enhancement of humoral or cellular immune response, to prevent or reduce opportunistic infections in immunodeficient patients, to prolong lymphopoiesis stimulation or to produce specific immune response or to broaden the repertoire of a specific immune response in human patients).

The fact that an intended use is recited in a claim does not negative the fact that the as-filed specification teaches how to make and use the composition. Furthermore, statements directed to a purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, *e.g.*, *In re Otto*, 312 F.2d 937, 938, 136 U.S.P.Q. 458, 459 (C.C.P.A. 1963) and M.P.E.P. § 2111.02. In this case, no transitional phrase is recited within the claim and the intended uses referred to in the preamble of the claims confers no structural differences between the compositions recited in claims 81-84 and independent claim 68. As the Patent Office is aware, when two claims in an application are duplicates, or else are so close

in content that they both cover the same thing, despite a slight difference in wording, it is proper to object to the other claim under 37 CFR 1.75 as being a substantial duplicate. In order to avoid the necessity of such an objection with the next Office Action, Applicants have canceled the claims as they are substantially duplicates of the claim from which they depend. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 56-58, 61-63, 66-71, 73-77, 80-85, 111 and 113 are rejected under 35 U.S.C. § 102(b) as anticipated by Namen *et al.* (U.S. Patent No. 5,328,988). The Office Action states that Namen *et al.* teach a substantially homogeneous recombinant human IL-7 polypeptide free of contaminating endogenous materials and that the human IL-7 comprises the amino acid sequence of residues 1-152 of Figure 5, which is identical to SEQ ID NO: 2 of the subject application. Claims 56-58, 61-63, 66-71, 73-75, 78-85, 111 and 113 are rejected under 35 U.S.C. § 102(b) as anticipated by Ho *et al.* (U.S. Patent No. 5,714,141). The Office Action indicates that the Ho *et al.* patent teaches the use of recombinant human IL-7 in a pharmaceutical composition to improve the potency of a vaccine and teaches the composition comprising IL-7 and the vaccine. Applicants respectfully assert that neither the Namen *et al.* patent nor the Ho *et al.* patent anticipates the claimed invention for the reasons that follow.

Applicants note that the Office Action argues that a compound and all its properties are inseparable (citing to *In re Papesch*) and that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer (citing to *Atlas Powder Co. v. Ireco, Inc.*). The Office Action further argues that Srinivasan *et al.* teach the recited structural feature/disulfide bond pattern and that this is evidence that the compositions of Namen *et al.* and Ho *et al.* are inherently the same as the composition of matter and pharmaceutical compositions recited within the currently pending claims.

Applicants respectfully assert that neither the Namen *et al.* patent nor the Ho *et al.* patent anticipate the claimed invention as both references fail to teach a composition of matter comprising a human or simian IL-7 conformer that comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said composition of matter is at least 98% by weight and wherein said

composition of matter is substantially free of IL-7 molecular variants or product related impurities. As noted in the as-filed application: "The present invention now shows, unexpectedly, that the long term activity of recombinant human IL-7 is mostly expressed by a specific 1-4; 2-5; 3-6 conformer. The present invention further shows that efficient drug substances should not only contain the above conformer as the major constituent, but should also be essentially devoid of other conformers or IL-7 molecular variants, previously considered as active products." (see page 3, lines 5-10). Thus, neither Namen *et al.* nor Ho *et al.* anticipate the claimed invention as the IL-7 compositions disclosed in the patents do not contain the claimed IL-7 conformer in amounts of at least 98% by weight nor are the IL-7 compositions of matter disclosed in Namen *et al.* or Ho *et al.* substantially free of IL-7 molecular variants or product related impurities.

With respect to the assertion that Srinivasan *et al.* teach the recited structural feature/disulfide bond pattern and that the IL-7 compositions of Namen *et al.* or Ho *et al.* inherently have this feature, Applicants again submit that this is not necessarily the case. As noted in the as-filed specification, the art generally recognizes the following disulfide bonding pattern: Cys: 1-6; 2-5; 3-4 and only computational modeling (*e.g.*, Srinivasan *et al.*) hypothesized the existence of the claimed IL-7 conformer having disulfide bonds at Cys: 1-4; 2-5; and 3-6 (specification at page 3, lines 12-21). Indeed, the conformation described in the *Protein Data Bank at Brookhaven National Laboratory* for IL-7 recognizes the following disulfide bonding pattern: Cys: 1-6; 2-5; 3-4 (see attached print-out for UniProtKB/Swiss-Prot Entry P13231 and as-filed specification at page 9, lines 19-22). Thus, it cannot be said that the IL-7 compositions of matter disclosed in either Namen *et al.* or Ho *et al.* would inherently contain the claimed conformer in amounts of at least 98% by weight and substantially free of IL-7 molecular variants or product related impurities.

Additionally, the as-filed specification has compared IL-7 compositions similar to those disclosed in Namen *et al.* or Ho *et al.* with IL-7 compositions corresponding to the claimed invention and identified differences between the compared compositions. As is indicated in the specification, purified IL-7 compositions comprising the claimed IL-7 conformers (containing the disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129); and 3-6 (Cys47-Cys141)) demonstrate biological activities that differ from other IL-7 compositions (see Examples H, I, and J; pages 59-64). These differing biological activities include reduced immunogenicity of the claimed composition or

composition of matter, increased CD4 T-cell counts in animals treated with the claimed composition or composition of matter, and irradiated animals treated with the claimed composition or composition of matter demonstrated increased CD4 cell counts for a longer period of time as compared to irradiated animals treated with other forms of IL-7 (Figure 13). Accordingly, it is respectfully submitted that compositions comprising the claimed IL-7 conformers or compositions of matter containing the claimed IL-7 conformers in amounts of at least 98% by weight and substantially free of IL-7 molecular variants or product related impurities differ from those taught in Namen *et al.* or Ho *et al.* and are not inherently disclosed in either of those references.

Applicants further submit a declaration by Dr. Michel Morre as additional evidence that the claimed IL-7 compositions of matter differ from those of the prior art and commercially available IL-7 compositions. As noted by Dr. Morre, the as-filed specification and the declaration present data that show that IL-7 expression in mammalian cells such as CHO or prokaryotic cells, such as *E. coli*, does not automatically lead to refolding of IL-7 corresponding to the claimed conformer and composition of matter. The declaration also indicates that the claimed composition of matter (corresponding to the claimed conformer and containing at least 98% of the claimed conformer by weight) differs from commercially available IL-7 preparations. Further, the declaration indicates that the claimed composition of matter would be expected to differ from those disclosed in the Namen *et al.* and Ho *et al.* patents. Finally, the as-filed specification and/or declaration indicate that IL-7 related impurities (*e.g.*, aggregates and other conformers), even in low amounts, trigger anti-IL-7 immunogenicity, which should be carefully monitored during clinical studies. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Claims 64 and 65 are rejected under 35 U.S.C. § 103(a) as obvious over Namen *et al.* (U.S. Patent No. 5,328,988) or Ho *et al.* (U.S. Patent No. 5,714,141) in view of Goeddel *et al.* (U.S. Patent No. 5,223,408). The Goeddel *et al.* patent is cited as teaching conjugating an IL-7 polypeptide with IgG1-Fc or albumin to increase half life. Claim 72 is rejected under 35 U.S.C. § 103(a) as obvious over Ho *et al.* (U.S. Patent No. 5,714,141) in view of Morozov *et al.* (U.S. Patent No. 5,728,680). The Office Action asserts that Morozov *et al.* teach pharmaceutical compositions for treating Hepatitis B virus infection that is formulated with excipients. Applicants respectfully assert that the claimed invention is not obvious over the cited references.

As noted above, neither Namen *et al.* nor Ho *et al.* teach a composition of matter comprising a human or simian IL-7 conformer, wherein said conformer comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount of said IL-7 conformer in said composition of matter is at least 98% by weight and wherein said composition of matter is substantially free of IL-7 molecular variants or product related impurities. Neither Goeddel *et al.* nor Morozov *et al.* cure this defect in the teachings of Namen *et al.* or Ho *et al.* As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention (*CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established in this matter.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/sl

Attachments: UniProtKB/Swiss-Prot Entry P13231
Declaration Pursuant to 37 C.F.R. §1.132 of Michel Morre

UniProtKB/Swiss-Prot entry P13232

Entry information

Entry name	**IL7_HUMAN**
Primary accession number	**P13232**
Secondary accession numbers	None
Integrated into Swiss-Prot on	January 1, 1990
Sequence was last modified on	January 1, 1990 (Sequence version 1)
Annotations were last modified on	June 10, 2008 (Entry version 86)

Name and origin of the protein

Protein name	**Interleukin-7 [Precursor]**
Synonym	**IL-7**
Gene name	**Name: IL7**
From	Homo sapiens (Human) [TaxID: 9606]
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.
Protein existence	1: Evidence at protein level;

References

[1] NUCLEOTIDE SEQUENCE [MRNA].
PubMed=2643102
Goodwin R.G., Lupton S., Schmierer A., Hjerrild K.J., Jerzy R., Clevenger W., Gillis S., Cosman D., Namen A.E.;
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Genome Res. 14:2121-2127(2004).

[4] DISULFIDE BONDS, AND MASS SPECTROMETRY.
DOI=10.1074/jbc.272.52.32995; PubMed=9407080
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Comments

- ***FUNCTION***: Hematopoietic growth factor capable of stimulating the proliferation of lymphoid progenitors. It is important for proliferation during certain stages of B-cell maturation.
- ***INTERACTION***:
P31785:IL2RG; NbExp=2; IntAct=EBI-80516, EBI-80475;
P16871:IL7R; NbExp=3; IntAct=EBI-80516, EBI-80490;
- ***SUBCELLULAR LOCATION***: Secreted.
- ***SIMILARITY***: Belongs to the IL-7/IL-9 family.
- ***WEB RESOURCE***: Name=Wikipedia; Note=Interleukin-7 entry;
URL="http://en.wikipedia.org/wiki/Interleukin_7";.

Copyright

Cross-references

Sequence databases	
EMBL	J04156; AAA59156.1; -; mRNA. M29053; AAC63047.1; -; Genomic_DNA. M29048; AAC63047.1; JOINED; Genomic_DNA. M29049; AAC63047.1; JOINED; Genomic_DNA. M29050; AAC63047.1; JOINED; Genomic_DNA. M29051; AAC63047.1; JOINED; Genomic_DNA. M29052; AAC63047.1; JOINED; Genomic_DNA. BC047698; AAH47698.1; -; mRNA.
PIR	A43527; A32223. B32223; B32223. C32223; C32223.
RefSeq	NP_000871.1; -.

UniGene	Hs.591873
3D structure databases	
PDB	1IL7; Model; -; A=26-177.
PDBsum	1IL7; -.
Protein-protein interaction databases	
DIP	DIP:3044N; -.
IntAct	P13232; -.
Organism-specific databases	
H-InvDB	HIX0025568; -.
HGNC	HGNC:6023; IL7.
GeneLynx	IL7; Homo sapiens.
GenAtlas	IL7.
MIM	146660; gene.
PharmGKB	PA29839; -.
Gene expression databases	
ArrayExpress	P13232; -.
CleanEx	HS_IL7; -.
GermOnline	ENSG00000104432; Homo sapiens.
Ontologies	
GO	GO:0005576; Cellular component: extracellular region *(traceable author statement from ProtInc).* GO:0005139; Molecular function: interleukin-7 receptor binding *(traceable author statement from ProtInc).* GO:0045453; Biological process: bone resorption *(inferred from sequence or structural similarity from UniProtKB).* GO:0007267; Biological process: cell-cell signaling *(traceable author statement from ProtInc).* GO:0006959; Biological process: humoral immune response *(traceable author statement from ProtInc).* GO:0043066; Biological process: negative regulation of apoptosis *(inferred fron sequence or structural similarity from UniProtKB).* GO:0009887; Biological process: organ morphogenesis *(traceable author statement from ProtInc).* GO:0030890; Biological process: positive regulation of B cell proliferation *(inferred from sequence or structural similarity from UniProtKB).* GO:0045582; Biological process: positive regulation of T cell differentiation *(inferred from sequence or structural similarity from UniProtKB).*
Family and domain databases	
InterPro	IPR001181; Interleukin-7. IPR000226; Interleukin_7_9.
PANTHER	PTHR10526; Interleukin-7; 1.
Pfam	PF01415; IL7; 1.

PIRSF	PIRSF001942; IL-7; 1.
PRINTS	PR00435; INTERLEUKIN7.
ProDom	PD013168; Interleukin-7; 1.
SMART	SM00127; IL7; 1.
PROSITE	PS00255; INTERLEUKIN_7_9; 1.
Genome annotation databases	
Ensembl	ENSG00000104432; Homo sapiens.
GeneID	3574; -.
KEGG	hsa:3574; -.
Phylogenomic databases	
HOGENOM	P13232; -.
HOVERGEN	P13232; -.
Other	
Implicit links to	GeneCards; SOURCE; BLOCKS; ProtoNet; ModBase; UniRef.

Keywords

3D-structure; **Cytokine**; **Glycoprotein**; **Growth factor**; **Secreted**; **Signal**.

Features

Key	From	To	Length	Description	FTId
SIGNAL	1	25	25		
CHAIN	26	177	152	Interleukin-7.	PRO_0000015623
CARBOHYD	95	95		N-linked (GlcNAc...) (Potential).	
CARBOHYD	116	116		N-linked (GlcNAc...) (Potential).	
CARBOHYD	141	141		N-linked (GlcNAc...) (Potential).	
DISULFID	27	166			
DISULFID	59	154			
DISULFID	72	117			
HELIX	28	41	14		
TURN	42	44	3		
HELIX	45	52	8		
STRAND	68	70	3		
HELIX	71	89	19		
STRAND	90	93	4		
HELIX	99	106	8		
HELIX	108	119	12		
HELIX	121	124	4		
TURN	141	144	4		
HELIX	147	172	26		

Sequence information

Length: **177 AA** [This is the length of the unprocessed precursor]

Molecular weight: **20187 Da** [This is the MW of the unprocessed precursor]
CRC64: **8FC5243F9169617F** [This is a checksum on the sequence]

```
        10         20         30         40         50         60
MFHVSFRYIF GLPPLILVLL PVASSDCDIE GKDGKQYESV LMVSIDQLLD SMKEIGSNCL

        70         80         90        100        110        120
NNEFNFFKRH ICDANKEGMF LFRAARKLRQ FLKMNSTGDF DLHLLKVSEG TTILLNCTGQ

       130        140        150        160        170
VKGRKPAALG EAQPTKSLEE NKSLKEQKKL NDLCFLKRLL QEIKTCWNKI LMGTKEH
```